

The use of conductometric assessments for development of pulsed release of lidocaine hydrochloride from thermosensitive N-isopropylacrylamide microgels

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Summary

The aim of present work was preliminary assessment of the conductivity changes in aqueous compartment, consisting of lidocaine hydrochloride, and N-isopropylacrylamide derivative microgel, during increasing the temperature between 25° and 42°C, as a prerequisite to demonstrate the possibility of applying this microgel for pulsed release of lidocaine hydrochloride, when increased temperature is applied. Conductivity of respective systems composed of polymer and lidocaine hydrochloride were assigned as PNM I-LD, PNM II-LD, and PNM III - LD: obtained values were in the ranges: 39,91 $\mu\text{S}/\text{cm}$ - 53,30 $\mu\text{S}/\text{cm}$ in the 25°C temperature, 46,14 $\mu\text{S}/\text{cm}$ - 56,16 $\mu\text{S}/\text{cm}$ in the temperature of 32°C, and 53,30 $\mu\text{S}/\text{cm}$ - 118,42 $\mu\text{S}/\text{cm}$ at 42°C.

During heating or cooling of the microgels derivatives of N-isopropylacrylamide, there is possibility to obtain pulsed release of lidocaine hydrochloride from the polymeric bead in the range between 25°C and 42°C, according to the conductivity measurements.

Key words: lidocaine hydrochloride, microgel, N-isopropylacrylamide, pulsed release, thermosensitivity, conductivity

INTRODUCTION

Lidocaine hydrochloride is usually applied as local anaesthetic, often in the oral cavity [1]. Dermal application of lidocaine is advised, when burn wounds occur, and the efficacy of the adrenaline-lidocaine subcutaneous infiltration was assessed in patient undergoing burn surgery, including the haemostatic effect of the infiltration [2]. The formulations of lidocaine are applied to decrease the pain caused by Herpes zoster infection, and postherpetic neuralgia [3]. Lidocaine is also used in mixtures with other local analgesics, like prilocaine for pain control in the course of transrectal ultrasound guided prostate biopsy [4], or for topical anesthesia of gingival mucosa in the form of eutectic system [5].

Mixture of lidocaine and epinephrine was assessed for pulpal anesthesia in stomatology [6]. The lidocaine possesses also interesting anti-inflammatory activity which may be considered as the additional synergistic feature, addressed to diseases with pain and inflammation [7]. Development of proper delivery systems for controlled and targeted delivery of lidocaine is of high importance, as there is possibility of severe cutaneous intoxication [8]. For development of lidocaine intra-oral, topical formulations, mucoadhesive polymers are extensively researched - the hydroxypropylcellulose, polyoxyethyleneglycol, polyacrylic resin, and polyvinylpyrrolidone were investigated [9].

Two phase, melt systems, containing lidocaine and thymol were evaluated for the topical application on the skin - 5% cream prepared with the systems was highly effective in the term of obtaining dermal anesthesia [10]. Contemporary some authors proposed binding of lidocaine hydrochloride in alginate microspheres [11]. Gorner proposed lidocaine-loaded biodegradable nanospheres for targeted analgesics delivery [12]. In the newer research the local implants were developed by Liu [13]. This implants consisted of polyanionic, i.e. carbopol hydrogels or polycationic, i.e. chitosan systems, and obtained release rates from the implants were described by the Higuchi model.

Thermosensitive sol-gel reversible hydrogels are still interesting polymers for development of the controlled drug delivery devices. The so called lower critical solution temperature (LCST), in which the transition point occurs, is in the range between 30 °C and 160 °C, with poly(N-vinylcaprolactam) and poly(vinyl pyrrolidone)

on the lowest and highest end of the scale respectively [14]. In case of poly(N-isopropylacrylamide) the precipitation in aqueous environment is visualized as opalescence in temperature above 32°C, according to the dehydration of the hydrophobic isopropyl groups during the coil-to-globule transition. For lidocaine, lidocaine hydrochloride, propranolol, propranolol hydrochloride, and cyanocobalamine Fundueanu and al. developed a stable form of microgel preparation [15]. Tasdelen evaluated a co-polymer of N-isopropylacrylamide and itaconic acid to enable the controlled release of lidocaine, and concluded that both temperature and pH influence the release process [16].

The conductometric analysis has a long history in the terms of indicating and assessment of different substances in aqueous media. The use of electroanalysis in biomedical science is developed for numerous application. New techniques involve miniaturized electrolytic conductivity probe with a wide range [17]. Electrochemical studies are often applied for the evaluation of micelle structures - Lorente et. al. exploited the conductometry for micelles containing tetracaine hydrochloride [18].

The characterization of microemulsions with diclofenac sodium was performed by the conductivity measurements, to evaluate the influence of water amount on the properties of the formulation [19]. In last decade Merclin and Beronius proposed interesting device for testing the structure and transport phenomena of electrolytes in liquid solutions, applying the lidocaine hydrochloride as model substance [20]. The idea of the device is based on the conductometric assessments.

The aim of the work was preliminary assessment of the conductivity changes in aqueous compartment, consisting of lidocaine hydrochloride, and N-isopropylacrylamide derivative microgel, during increasing the temperature between 25° and 42°C, as a prerequisite to demonstrate the possibility of applying this microgel for pulsed release of lidocaine hydrochloride, when increased temperature is applied.

MATERIAL AND METHODS

Material

pNIPAM microgels particles derived from previous works in the field of polymer science. The polymers were synthesized by surfactant free emulsion

polymerization (SFEP) in de-ionized water at 343 K, under an inert nitrogen atmosphere. The characteristics of the polymers is presented in the Table 1. Lidocaine hydrochloride was purchased from Sigma-Aldrich. Purified water obtained from the TKA DI 6000 system (Germany) was used for all the experiments. N-isopropylacrylamide 99%, initiators and co-monomer were obtained from commercial suppliers.

Composition of assessed systems

The composition of evaluated systems was presented in the Table 2. The respective mass of lidocaine hydrochloride was mixed with the dispersion of synthesized polymer. The mixing period was maintained for 24 h, at the room temperature.

The conductivity assessments

The conductivity was assessed in evaluated systems, at specified temperatures, i.e.: 25°C, 32°C, and 42°C. The conductivity of pure solutions of lidocaine hydrochloride was assessed in concentrations applied in the systems. The SevenMulti Metler Toledo, with conductivity segment TDS/SAL/resistivity with the conductivity sensor InLab 730, NTC, 0,001-1000 mS/cm, measurements range -5 °C – 100 °C was applied.

RESULTS

The conductivity of evaluated systems was in the range between 8,73 $\mu\text{S}/\text{cm}$ and 44,63 $\mu\text{S}/\text{cm}$ in the case of synthesized microgels PNM I, PNM II, and PNM III. For the 25°C temperature the conductivity was 8,73 $\mu\text{S}/\text{cm}$ - 11,79 $\mu\text{S}/\text{cm}$, whereas when temperature increased, the conductivity increased as well - up to 10,25 $\mu\text{S}/\text{cm}$ - 13,31 $\mu\text{S}/\text{cm}$ range for the 32°C, and up to the range 22,08 $\mu\text{S}/\text{cm}$ - 44,63 $\mu\text{S}/\text{cm}$ for the highest assessed temperature - 42°C - column 1 in Table 3. The respective conductivities for the solution of lidocaine hydrochloride, gathered in the column 2 of Table 3 were in following ranges: 41,46 $\mu\text{S}/\text{cm}$ for 25°C, 41,62 $\mu\text{S}/\text{cm}$ for 32°C, and 55,66 $\mu\text{S}/\text{cm}$ for 42°C.

Also the conductivity of respective systems composed of polymer and lidocaine hydrochloride were measured and presented in column 3, Table 3. In this systems assigned as PNM I-LD, PNM II-LD, and PNM III - LD, the obtained values were in the ranges: 39,91 $\mu\text{S}/\text{cm}$ - 53,30 $\mu\text{S}/\text{cm}$ in the 25°C temperature, 46,14 $\mu\text{S}/\text{cm}$ - 56,16 $\mu\text{S}/\text{cm}$ in the temperature of 32°C. When the temperature increased to 42°C, the conductivity of complexed systems was in the range 53,30 $\mu\text{S}/\text{cm}$ and 118,42 $\mu\text{S}/\text{cm}$.

The theoretically estimated values enumerated in column 4 of the Table 3 based on the assumption of additive characteristics of the conductivity in this systems. The calculated values for the PNM I - LD, PNM II - LD, and PNM III - LD systems were in the range of 50,19 $\mu\text{S}/\text{cm}$ - 53,25 $\mu\text{S}/\text{cm}$ at 25°C, 51,87 $\mu\text{S}/\text{cm}$ - 66,28 $\mu\text{S}/\text{cm}$ at 32°C, and 77,74 $\mu\text{S}/\text{cm}$ - 100,29 $\mu\text{S}/\text{cm}$ at 42°C. In the last two columns, namely number 5 and 6, the differences between measured and calculated values were presented in absolute numbers and as the percentage values.

DISCUSSION

The microgel particles possess an interesting property of collapsing and expanding itself, usually in the aqueous environment, when the temperature increases or decreases. According to that fact, the availability of the functional groups would be limited or enhanced, depending on the degree of expansion of the polymeric net in the defined temperature conditions. This fact should have consequences in binding of other substances, like biologically actives, protein molecules, drugs, etc. In this research the influence of temperature on the conductivity of polymer - water soluble drug systems was evaluated, as a prerequisite to discuss the possibility of pulsed release of that drug from proposed formulation.

As it can be seen from the Fig. 1 the conductivity of polymer PNM I and PNM III increases slowly with the increase in temperature. Additionally the increase of the conductivity has similar course like in the case of lidocaine hydrochloride solution. However in the case of PNM II the increase is much harder expressed. This may lead to the conclusion, that the increase of temperature leads to increased activity of ionic groups in the PNM II polymer, and this information would be applicable for development of the pulsed release system.

The comparison of the conductivity changes of the components in aqueous systems with the changes in conductivity of resulting polymer-drug systems gives important information. According to the data presented on the graph, in Fig. 2, the systems with PNM II and PNM III polymer are characterized by moderate variability, when the increased temperature is applied. However, in the case of PNM I - LD system, the characteristic increase in the conductivity is observed, which reflects the changes in the conductivity for the solution of lidocaine hydrochloride.

In the case of PNM II - LD also the consequent increase of conductivity was observed, but not so remarkable, as in the case of PNM I - LD. Curiously, when the temperature of PNM III - LD system increased, its conductivity in the first step decreased from 52,29 $\mu\text{S}/\text{cm}$ to the 49,24 $\mu\text{S}/\text{cm}$, and then increased to 60,08 $\mu\text{S}/\text{cm}$.

When data from table 3, column 6 are compared, some irregularities are observed, considering the predicted and assessed values of conductivity. For PNM I - LD mixtures, the measured conductivity at 25°C was almost 26% lower than that calculated. So it may be assumed that in this conditions, part of the lidocaine hydrochloride is bonded to the polymer, or its ionization decreased. However at higher temperatures, the measured values are almost 8% and 33% higher, comparing to the theoretically calculated, so there is increase in the presence of ionized individuals in the solution. It should be noted, that this interaction was observed when the polymer synthesized with acidic initiator was applied - so the ionic interaction may be involved.

The PNM II - LD system behaves oppositely - the conductivity consequently decreases, with the temperature increase, comparing the predicted and measured values, from ca. 26%, through 44%, to 88%.

Regarding the alkali character of the initiator applied in the synthesis, this is logical result of the interaction between the polymer and drug. There are data from present experiment, which should be further evaluated, namely the influence of the increased lipophilicity of PNM III on the conductivity of related system with lidocaine hydrochloride. According to acquired data, when the temperature increases, the conductivity falls down in this system, when is compared to the predicted values. Probably the opening of lipophilic polymer structure inhibits the movement of some ions in the polymeric matrix, attracting them to the net, or slowing down the movement of the particles.

The proposed relations in a microgel particle, when the temperatures are changing are presented on Fig. 3. The $K_{(25)}$, $K_{(32)}$, and $K_{(42)}$ values represent in our study the affinity of the drug to the microgel in increasing temperatures, according to the conductivity measurements. The K values differ in various systems, depending both on the applied system and temperature of assessments. When PNM I - LD system is considered, the values are in following pattern: $K_{(25)} < K_{(32)} < K_{(42)}$. For PNM II and PNM III systems the values reach the order $K_{(25)} > K_{(32)} > K_{(42)}$.

CONCLUSIONS

1. During heating or cooling the microgels, derivatives of N-isopropylacrylamide, there is possibility to obtain pulsed release of lidocaine hydrochloride from the polymeric bead in the range between 25°C and 42°C, according to the conductivity measurements.

2. In the case of anionic initiator the observed conductivity changes suggest that the N-isopropylacrylamide polymer may be involved in devices, which release lidocaine hydrochloride, when increased temperature is applied.

3. Oppositely, the N-isopropylacrylamide derivatives synthesized with alkali initiator, or characterized by increased lipophilicity, may exhibit the pulsed release during cooling the polymeric beads.

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Tabela 1. Charakterystyka zastosowanych w badaniach polimerów

Table 1. Characteristics of polymers applied in the present study

Typ mikrożelu Type of microgel	Zastosowane grupy funkcyjne Implemented functional groups
PNM I	Grupa kwasowa/Acidic group
PNM II	Grupa zasadowa/Alkalic group
PNM III	Grupa kwasowa & Grupa lipofilowa/Acidic group & Lipophilic group

Tabela 2. Skład badanych układów

Table 2. The composition of evaluated dispersions

Skład Composition	PNM-I [mg]	PNM-II [mg]	PNM-III [mg]	LD [mg]	Woda Water [g]
PNM I - LD	5,00	-	-	5,00	60,00
PNM II - LD	-	5,00	-	5,00	60,00
PNM III LD	-	-	5,00	5,00	60,00
LD	-	-	-	5,00	60,00

PNM I, PNM II, PNM III - polimery/polymers,

LD - chlorowodorek lidokainy/lidocaine hydrochloride

Tabela 3. Przewodnictwo badanych systemów, w których zastosowano polimery i chlorowoderek lidokainy

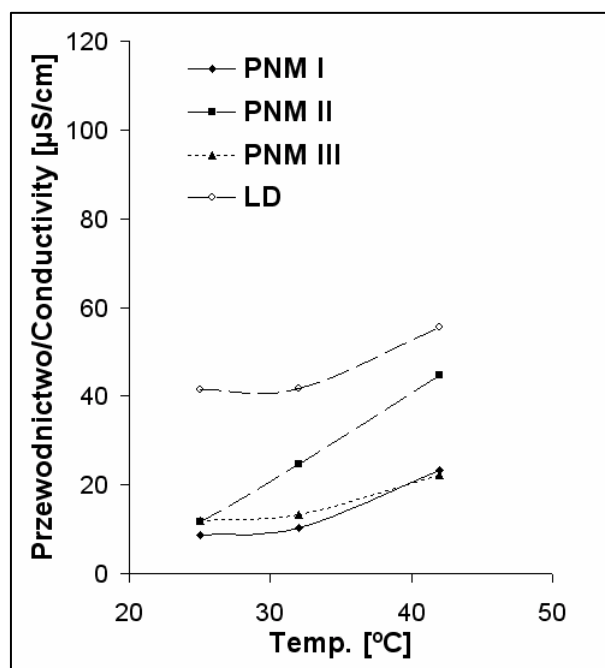
Table 3. Conductivity of assessed systems with polymers and lidocaine hydrochloride

Temperatura Temperature [°C]	Typ Type	Przewodnictwo/Conductivity [μS/cm]					
		1	2	3	4	5	6
		Mikrożel Microgel	LD	Wartości zmierzone LD + mikrożel Measured values LD + microgel	Wartości obliczone LD + mikrożel Estimated values LD + microgel	Różnica Poz. 4 i 3 Difference It. 4 and 3	Przyrost (+) lub spadek (-) Increase (+) or decrease (-) [%]
25	PNM I	8.73	41.46	39.91 ±1.97 SD	50.19	-10.29	-25.78
32	PNM I	10.25	41.62	56.16 ±0.73 SD	51.87	4.29	+7.65
42	PNM I	23.24	55.66	118.42 ±0.49 SD	78.90	39.52	+33.37
25	PNM II	11.61	41.46	42.24 ±0.57 SD	53.07	-10.83	-25.65
32	PNM II	24.66	41.62	46.14 ±1.18 SD	66.28	-20.14	-43.66
42	PNM II	44.63	55.66	53.30 ±0.60 SD	100.29	-46.99	-88.16
25	PNM III	11.79	41.46	52.26 ±1.58 SD	53.25	-0.99	-1.89
32	PNM III	13.31	41.62	49.24 ±0.75 SD	54.93	-5.69	-11.55
42	PNM III	22.08	55.66	60.08 ±0.41 SD	77.74	-17.66	-29.40

PNM I, PNM II, PNM III - polimery/polymers,

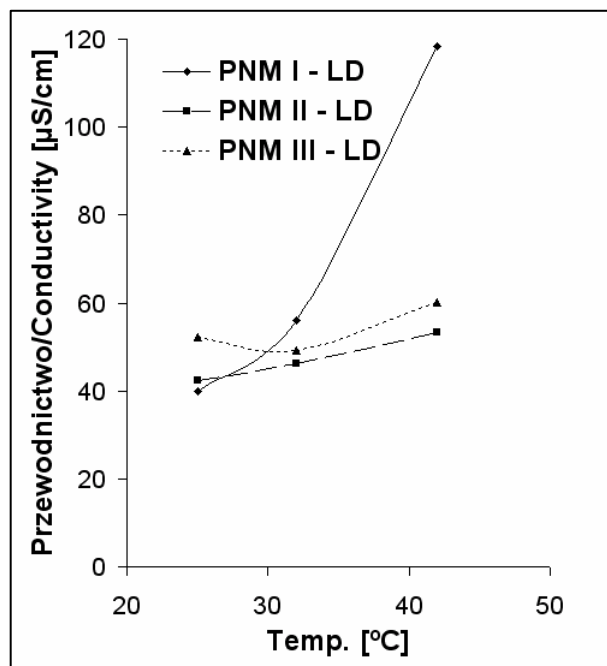
LD - chlorowoderek lidokainy/lidocaine hydrochloride,

SD - odchylenie standardowe/standard deviation



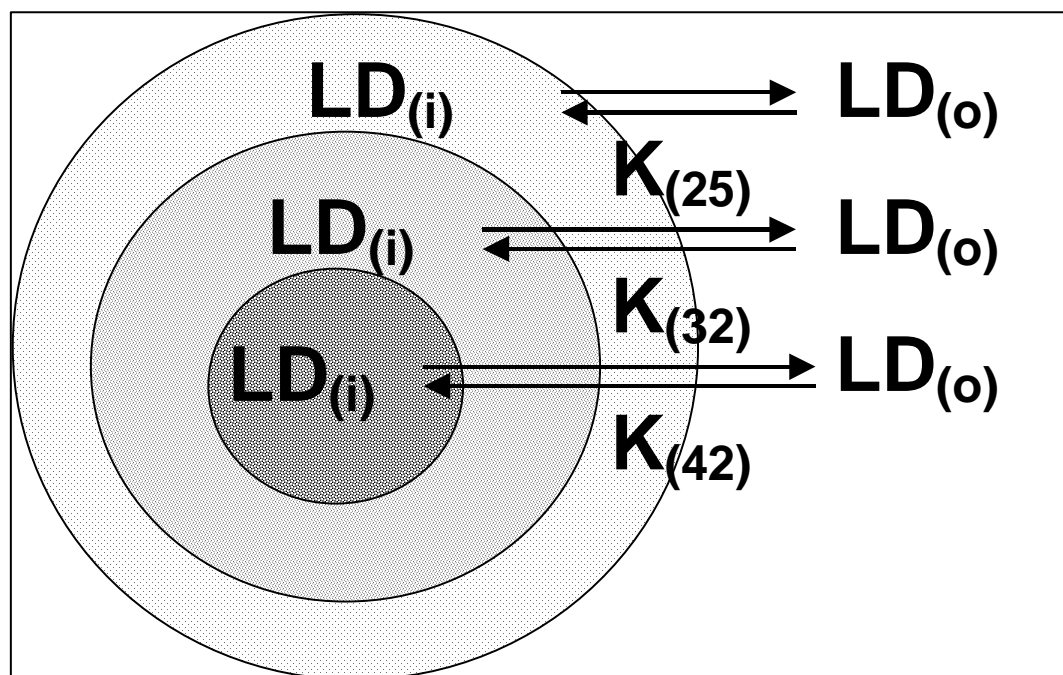
Ryc. 1. Wpływ temperatury na przewodnictwo badanych polimerów i chlorowodoru lidokainy, PNM I, PNM II, PNM III - polimery, LD - chlorowodorek lidokainy

Fig. 1. Influence of temperature on the conductivity of assessed polymers and lidocaine hydrochloride, PNM I, PNM II, PNM III - polymers, LD - lidocaine hydrochloride



Ryc. 2. Wpływ temperatury na przewodnictwo badanych systemów zawierających polimery i chlorowodorek lidokainy, PNM I - LD, PNM II - LD, PNM III - LD: odpowiednie mieszaniny polimerów i chlorowodoru lidokainy

Fig. 2. Influence of temperature on the conductivity of assessed systems containing polymers and lidocaine hydrochloride, PNM I - LD, PNM II - LD, PNM III - LD: respective mixtures of polymers and lidocaine hydrochloride



Ryc. 3. Wizualizacja wiązania chlorowodoru lidokainy z mikrożelami, w zależności od temperatury pomiaru. $LD_{(i)}$ - chlorowodorek lidokainy związany w mikrosferach polimerowych, $LD_{(o)}$ - chlorowodorek lidokainy poza mikrosferami polimerowymi, gęstość zacielenia odpowiada zmianom morfologicznym zachodzącym w trakcie podgrzewania i chłodzenia rozproszenia mikrosfer polimerowych

Fig. 3. Visualization of the influence of temperature on the binding of lidocaine hydrochloride with microgels. $LD_{(i)}$ - lidocaine hydrochloride bonded to polymeric microspheres, $LD_{(o)}$ - lidocaine hydrochloride outside the polymeric microspheres, density of the dots represents the changes during heating and cooling the microspheres